REMARKS

Status of the claims

Claims 1-25 and 39-85 are pending. Claims 1-25 and 39-50 are withdrawn from further consideration. Claims 26-38 have been cancelled. Claims 51-85 are rejected. By this amendment, claims 51-85 are cancelled without prejudice or disclaimer, and new claims 86-133 have been added.

No new matter is added by this amendment. The new claims are supported in the specification and in the previously pending claims as follows. Claim 86 is supported, for example, at page 14, lines 5-8 ("specifically recognizes a cancer cell and does not recognize a normal non-cancerous cell"), page 11, lines 4-6; Examples 4-9, including page 66, lines 1-2; page 10, lines 19-28; page 19, lines 2-5; page 48, line 19 to page 49, line 20; page 33, lines 22-25 (describing a monomer scFV in SEQ ID NO:13); Example 7 (describing the preparation of monomer scFv, including amplification of heavy and light chain variable regions using specified primers); page 64, lines 16-18; page 17, lines 8-9; page 82, lines 1-3; page 41, lines 22-23; page 33, lines 4-6; page 38, lines 13-20; page 39, lines 29-30; page 10, lines 19-28; page 19, lines 2-5; page 48, line 19 to page 49, line 20).

The amino acid sequences of the H chain V region and the L chain V region of the polypeptide in SEQ ID NO: 13 are fully described in the specification as follow:

First, the specification states at col. 19, lines 5-6 that SEQ ID NO:13 shows an H11-scFv2 construct having the form VL-linker-VH (indicating the orientation and general configuration of the sequences encoded in SEQ ID NO:13). Example 7 (specification at 73-74) describes the preparation of a monomer scFv construct as follows:

(a) PCR reactions were carried out using primers 1 and 6 for the kappa (light chain) monomer and primer 4 and 5 for the mu (heavy chain) monomer. As noted in Table 7 (specification at page 74), primer 1 additionally carries a BbsI restriction site, primer 6 carries a BspE1 restriction site, primer 5 carries a BspE1 restriction site, and primer 4 carries a BamHI restriction site. The specation notes that primers 5 and 6 also contain nucleotides that encoded a

$(SGGGG)_3$ linker. The specification further notes that vector pSJF1 carries OmpA signal peptide sequences (see specification at page 74,, lines 9-12; Figure 8).

Thus, the amplified fragments have the following configurations:

kappa (light chain): 5'--primer 1 with 5'-BbsI site-kappa (light chain V region) sequence-partial linker sequence-Primer 6 with 3' BspEI site--3'

mu (heavy chain): 5'--primer 5 with 5'-BspEI site-partial linker sequence-mu (heavy chain variable region) sequence- Primer 4 with 3' BamHI site--3'

(b) Following PCR, the amplified fragments were digested with BbsI and BspE1 (kappa) or BspEI and Ban HI (mu), and the fragments were ligated into the expression vector pSJF1 (see Figure 8), which was prepared by digestion with BamH1 and BbsI.

The following diagram depicts the fragments that were ligated together:

vector -BbsI site-3' + 5'--primer 1 with 5'-BbsI site-kappa (light chain V region) sequence-partial linker sequence-Primer 6 with 3' BspEI site--3' + 5'--primer 5 with 5'-BspEI site-partial linker sequence-mu (heavy chain variable region) sequence- Primer 4 with 3' BamHI site--3' + 5' end-BamHI site-vector.

Thus, it is evident that the boundaries of the vector sequence, light chain variable region, linker, heavy chain variable region and vector are defined by the primers as described above and diagrammed on the Figure. The sequence of the linker portion and the presence of the OmpA signal peptide sequence (in vector sequences) are also described in the specification. Thus, by locating (a) the primer sites in the nucleotide sequence of SEQ ID NO:13, (b) the sequence of the OmpA signal peptide and (c) the linker sequence, it is straightforward to locate the boundaries of the light chain and heavy chain variable regions encoded by the polynucleotide sequence of the scFv shown in SEQ ID NO:13.

First, it is evident that the linker sequence--a $(SGGGG)_3$ linker -- is located at nucleotides 433 through nucleotides 477 (amino acids 145 to 160). It is further evident that the OmpA signal

peptide sequence (which is well known in the art)[1] begins at nucleotide 7 a(amino acid 2) and extends through nucleotide 69 (amino acid 23).

The light chain variable region, including part of the linker, is defined by primer sequences 1 and 6 as follows: primer 1 is evident from nucleotide 64 to nucleotide 88 and primer 6 is evident from nucleotide 406 to nucleotide 450 (primer 6 contains part of the linker sequence).

The heavy chain variable region, including part of the linker, is defined by primer sequences 4 and 5 as follows: primer 5 is evident from nucleotide 446 to nucleotide 498 (primer 5 contains part of the linker sequence) and primer 4 is evident from nucleotide 834 through nucleotide 858 (primer 4 contains a BspE1 restriction site).

Combination of the above information provides the following map: the OmpA signal peptide sequence begins at nucleotide 7 (amino acid 2) and extends through nucleotide 69 (amino acid 23), the variable region light chain sequences begin at nucleotide 70 (amino acid 24) and continue to nucleotide 432 (amino acid 144), the linker sequence begins at nucleotide 433 (amino acid 145) and spans to nucleotide 477 (amino acid 159) and the heavy chain variable region begins at nucleotide 478 (amino acid 159) and ends at nucleotide 851 (amino acid 284). The remaining sequences comprise the restriction site at the end of primer 4, and vector sequences (as is evident based on the description in the specification).

Claims 87 to 114 are supported in the specification and pending claims as follows: claim 87 at page 1, lines 9-11; page 19, lines 2-5; Tables 4, 5, 6; page 72, lines 14-27; page 30, lines 14-27; page 31, lines 11-16; page 19, lines 15-25; claim 88 at page 15, lines 5-9; page 38, lines 12-14; claim 89 (same as for claim 88); claim 90 (original claim 27; page 38, lines 12-14); claim 91 (page 38, lines 24-30; same as for claim 90); claim 92 (page 41, lines 4-13; page 40, lines 16-24; original claims 31-32; page 39, lines 14-17); claim 93 (page 40, lines 16-24; page 41, lines 21-24); claim 94 (same as claim 93); claim 95 at, e.g., page 31, lines 24-28; page 30, lines 14-27; claim 96 at, e.g., page 11, lines 3-8; pages 31, lines 1-9; claim 97-102 (see support for claim

[1] *See, e.g.,* U.S. Patent No. 4,757,013 (*see especially* Figure 32).

27; claim 96 at, e.g., page 11, lines 3-8; pages 31, lines 1-9; claim 97-102 (see support for claim 96);claim 103 (page 38, lines 24-28; page 31, lines 1-7; page 30, lines 18-24); claim 104 (same as for claim 103); claim 105 (page 41, lines 21-24; page 19, lines 6-14; original claim 2); claim 106 (same as for claim 105; original claim 6); claim 107 (same as for claim 105; original claim 7); claim 108 (same as for claim 69; original claim 9); claim 109 (same as for claim 105; original claim 12); claim 110 (same as for claim 105; original claim 16); claim 111 (page 10, lines 25-28; page 38, lines 13-20); claim 112 (page 28, line 12, lines 13-28); claim 113 (page 29, lines 5-7); claim 114 (page 28, lines 14-25); claim 115 (page 42, lines 23-26); claim 116 (page 42, lines 28-29); claim 117 (page 46, lines 3-5); claim 118 (original claim 37); claim 119 (page 41 line 28-page 42, line 3); claim 120 (page 27, line 9 et seq); claim 121 (page 33, lines 29-34; page 41, lines 21-24); claim 22 (page 33, lines 21-25; page 41, lines 21-24); claim 123 (same as claim 86); claim 124 (page 34, lines 28-29; page 41, lines 21-24); claim 125 (page 28, lines 3-12; page 41, lines 21-24); claim 126 page 15, line 4; page 41, lines 21-24); claim 127 (same as claims 86 and 87); claim 128 (page 31, lines 11-16; page 41, lines 21-24); claims 129 (page 31, lines 14-16; page 41, lines 21-24); claim 130 (page 30, lines 14-15; page 41, lines 21-24); claim 31 (same as claim 129); claim 132 (page 19, lines 3-5; page 29, lines 26-30); claim 133 (page 36, lines 1-2).

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application.

Interview

Applicants thank the Examiner for extending the courtesy of the helpful interview with Applicants' representative Gladys H. Monroy, and Bill Herman, on July 24, 2002 with Primary Examiner Caputa. This response reflects the results of that interview.

Applicants note that new claim 89 now recites SEQ ID NO:19, as requested by the Examiner during the interview.

Rejections under 35 U.S.C. §112, second paragraph (indefiniteness)

Claims 51-85 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

A. Claim 51 is rejected as allegedly indefinite on the ground that it is allegedly unclear "as to what entity the antigen binding fragment competitively inhibits." Office Action at 2. Applicants note that claim 51 has been canceled. Applicant will discuss the rejection in the context of the new claims, e.g., new claim 86, to the extent that the rejection may be deemed to apply thereto. Claim 86 now recites that antigen binding polypeptide competitively inhibits specific binding of an ScFv or antibody to a cancer cell surface epitope, wherein the ScFv or antibody is comprised of the amino acid sequences of the H chain V region and the L chain V region of the polypeptide in SEQ ID NO:13, and wherein the antigen binding polypeptide specifically recognizes a cancer cell surface and does not recognize a normal non-cancerous cell surface. Applicants believe that this amendment addresses the Examiner's concern that the claim does not indicate which entity the antigen binding fragment competitively inhibits. Withdrawal of this rejection is respectfully requested.

B. Claim 51 is rejected as allegedly indefinite because it is allegedly not clear "what the metes and bounds are of the "fragment" of the antibody whose Lv and Hv are comprised in SEQ ID NO:14. Applicants note that claim 51 has been cancelled. The new claims no longer recite the term "fragment". For example, new claim 86 requires a ScFv or antibody comprised of the amino acid sequences of the H chain V region and the L chain V region of the polypeptide in SEQ ID NO:13. Applicants note that one of ordinary skill in the art would consider the amino acid sequences of the H chain V region and the L chain V region of the polypeptide in SEQ ID NO:13 to be fully described in the specification, as discussed above (see pages 8-10). As such,

Applicants submit that the metes and bounds of the new claims are clear. Withdrawal of this rejection is respectfully requested.

C. Claim 59 is rejected as allegedly indefinite because it is allegedly "not clear which antibody fragment is inhibited by the 'antigen binding fragment encoded by the first polynucleotide". Office Action at 2. Applicants note that claim 59 has been canceled, and the new claims do not include the offending language. Accordingly, Applicants believe that this rejection is moot, and withdrawal of this rejection is respectfully requested.

D. Claims 59 and 64-68 are rejected as allegedly indefinite because the metes and bounds of stringent conditions are allegedly not clearly set out in the claims. Claim 59 and 64-68 have been canceled. Applicants will address the rejection to the extent that it may be deemed to apply to the new claims. Applicants respectively traverse this rejection.

Applicants respectfully submit that the meaning of stringent conditions is well known to one of ordinary skill in the art. Hybridization conditions are discussed in great detail in the specification (see, e.g., page 41, lines 5-13) and in such standard sources as the cloning manuals, *Molecular Cloning: A Laboratory Manual* by Sambrook et al. (1989) and *Current Protocols in Molecular Biology* by Ausubel et al. (1987). However, to clarify the meaning of "stringent conditions", new claim 92 now recites that stringent conditions comprise 0.1X SSC, 75% formamide and incubation at 68°C. Support for the amendment is found at page 41, lines 4-13. Applicants believe that this amendment addresses the Examiner's concern. Withdrawal of this rejection is respectfully requested.

E. Claim 51 (and the dependent claims therefrom) are rejected as allegedly indefinite because it is allegedly unclear "if the tumor cell surface epitope that competitively inhibits specific binding is the same as the hexapeptides [sic: heptapeptides] displayed on the phage." Office Action at 2.

As noted above, claim 51 has been canceled. Applicants will address this rejection in the context of new claim 88, to the extent that the rejection is deemed to apply thereto.

Applicants respectfully disagree that claim 88 is unclear. Claim 86 recites that the antigen binding polypeptide competitively inhibits specific binding of an ScFv or antibody to a cancer cell surface epitope. Dependent claim 88 states an additional requirement: that the antigen binding polypeptide specifically recognizes a heptapeptide as described in the remainder of claim 86. Similarly, the specification describes that the H11 antibody and ScFv specifically recognize the heptapeptides (see, e.g., pages 15-16), as well as binding to epitopes on a variety cancer cell surfaces and not recognizing a variety of non-cancerous cells (see, e.g., Examples). Thus it is evident that the cancer cell surface epitope and the heptapeptides are different entities, and are not the same as suggested by the Examiner. Withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. §112, first paragraph (written description)

Claims 51, 59 and 69-84 are rejected under 35 U.S.C. 112, first paragraph, for alleged lack of written description. Specifically, the Examiner states that the claims still require availability of the antigen because the claims allegedly "do[es] not provide a nexus between the claimed antibody and the antibody having SEQ ID NO:14". Office Action at 3. Applicants note that claims 51, 59 and 69-84 have been cancelled. Applicants will address the rejection in the context of the new claims, to the extent that it may be deemed to apply thereto. Applicants respectfully traverse this rejection.

Applicants respectfully disagree that the availability of the antigen is required in order to determine whether one antigen binding fragment "competitively inhibits binding to a cancer cell surface epitope" recognized by a second antigen binding fragment. However, new claim 86 now clarifies that the antigen binding polypeptide competitively inhibits specific binding of an ScFv or antibody to a cancer cell surface epitope, wherein the ScFv or antibody is comprised of the amino acid sequences of the H chain V region and the L chain V region of the polypeptide in SEQ ID NO:13, and wherein the antigen binding polypeptide specifically recognizes a cancer cell surface and does not recognize a normal non-cancerous cell surface. Applicants submit that

this amendment addresses the Examiner's concern. Withdrawal of this rejection is respectfully requested.

CONCLUSION

In light of the Amendments and the arguments set forth above, Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

In the unlikely event that the Fee Transmittal is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 316082000121. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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